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10/619,820	07/14/2003	Vivian Liu	57000-20002.00 8575	
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Kelvan Patrick Howard		BARNHART, LORA ELIZABETH		
MDS SCIX 1170 Veteran's	Blvd.		ART UNIT	PAPER NUMBER
Suite 200 South San Francisco, CA 94080		1651		
			DATE MAILED: 04/18/2006	5

Please find below and/or attached an Office communication concerning this application or proceeding.

		Application No.	Applicant(s)				
Office Action Summary		10/619,820	LIU ET AL.				
		Examiner	Art Unit				
_		Lora E. Barnhart	1651				
Period fo	The MAILING DATE of this communication or Reply	n appears on the cover sheet	with the correspondence ac	idress			
WHIC - Exter after - If NO - Failu Any (ORTENED STATUTORY PERIOD FOR REHEVER IS LONGER, FROM THE MAILIN nsions of time may be available under the provisions of 37 C SIX (6) MONTHS from the mailing date of this communication period for reply is specified above, the maximum statutory per to reply within the set or extended period for reply will, by reply received by the Office later than three months after the end patent term adjustment. See 37 CFR 1.704(b).	IG DATE OF THIS COMMUN FR 1.136(a). In no event, however, may a on. period will apply and will expire SIX (6) MO statute, cause the application to become	IICATION. a reply be timely filed DNTHS from the mailing date of this c ABANDONED (35 U.S.C. § 133).				
Status							
1)⊠	Responsive to communication(s) filed on	25 January 2006.					
		This action is non-final.					
3)	Since this application is in condition for all	nis application is in condition for allowance except for formal matters, prosecution as to the merits is					
	closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.						
Dispositi	on of Claims						
4) 🛛	Claim(s) 1-23,36 and 37 is/are pending in	the application.					
•	4a) Of the above claim(s) is/are wit		•				
	Claim(s) is/are allowed.						
	6)⊠ Claim(s) <u>1-23,36 and 37</u> is/are rejected.						
7)	Claim(s) is/are objected to.	·					
8)	Claim(s) are subject to restriction a	and/or election requirement.					
Applicati	on Papers			·			
9)	The specification is objected to by the Exa	miner.					
• —	The drawing(s) filed on is/are: a)		o by the Examiner.				
,	Applicant may not request that any objection to						
	Replacement drawing sheet(s) including the co			FR 1.121(d).			
·11)	The oath or declaration is objected to by the	ne Examiner. Note the attach	ed Office Action or form P	TO-152.			
Priority u	ınder 35 U.S.C. § 119						
	Acknowledgment is made of a claim for fo		§ 119(a)-(d) or (f).				
	1. Certified copies of the priority documents		Application No.				
	2. Certified copies of the priority docu3. Copies of the certified copies of the			Stage			
	application from the International B			olugo			
* 5	See the attached detailed Office action for	•	ot received.				
		·					
Attachmen	t(s)						
	e of References Cited (PTO-892)	4) 🔲 Interviev	v Summary (PTO-413)				
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) Paper No(s)/Mail Date							
	nation Disclosure Statement(s) (PTO-1449 or PTO/S r No(s)/Mail Date <u>2/2/04, 3/1/04</u> .	5B/08) 5)		0-102)			
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DETAILED ACTION

The reply received 1/25/06 amending claim 3, canceling claims 24-35, and adding claims 36 and 37 is acknowledged. Claims 1-23, 36, and 37 are currently pending.

Applicant should note that the examiner in this case has changed.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-23, 36, and 37 in the reply filed on 1/25/06 is acknowledged.

Applicant's election the species "signal transduction," "complex impedance," "resistance," "admittance," and "a ligand" in the reply filed on 1/25/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In the interest of compact prosecution, the election of "signal transduction" in claims 2 and 15 has been interpreted as an election of "signal transduction from ligand/receptor interactions."

Examination will commence on claims 1-23, 36, and 37 ONLY.

Claim Objections

Claims 1-23, 36, and 37 are objected to because of various informalities, discussed below. Appropriate correction is required.

In claim 1, line 3, there should be a comma after "stimulus."

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In claims 2-23, there should be a comma after the recitation of the parent claim, e.g. "The method of claim 1, wherein..." or "The method of claim 1, further comprising..."

The preamble to claim 1 is rather wordy; the examiner suggests the claim be amended to recite, "A label-free method for the classification of cellular events by the measurement of changes in the electrical properties of cells..."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23, 36, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining whether a few G protein-coupled receptors (GPCRs) and a few protein tyrosine kinase receptors (PTKRs) are activated within a few cell types under some conditions, does not reasonably provide enablement for determining whether any given cellular event is occurring within a cell under any given conditions. Furthermore, the specification is not enabling for determining whether any given event related in any way to any given receptor is occurring within any given cell under any given conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and to use the invention commensurate in scope with these claims.

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The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims have been interpreted (see rejections under section 112, second paragraph, below) as being broadly drawn to methods for determining whether a particular cell is undergoing a particular cellular event (for example, signal transduction arising from interactions between receptors and their ligands) by culturing cells in a vessel of some type; applying current to the medium and cells within said vessel; measuring a particular electrical property (for example, complex impedance) within the culture vessel; contacting the cells with a stimulus (for example, a putative ligand to one of the receptors known to be expressed by the cell); again applying current; measuring the same electrical property again at various time points, organizing the data from said measurements; comparing these data to some standard sets of data previously collected from cells in which known events were occurring; and using these comparisons to determine which events, if any, occur in the test cells. While applicants elected "signal transduction from ligand/receptor interactions" as the species of cellular event, this limitation has not been incorporated into all of the claims, so those claims

that do not specifically require that the event is "signal transduction from ligand/receptor interactions" must be interpreted broadly to encompass all events.

By applicant's own admission, the scope of the disclosure is limited to the use of the instant method for determining whether particular receptors have been activated and, in fact, to a few receptors in particular (Specification, paragraph 0001, lines 6-9). The inclusion of various examples not dealing specifically with receptor activation is noted (paragraphs 0048-0062), but these are clearly prophetic examples that suggest alternative uses for the claimed method, not specific guidance for performing the method to determine whether, for example, apoptosis is occurring in a given cell. There is no reasonable expectation, in light of the specification and the prior art, that each and every possible cellular event (for example, DNA replication, ubiquitination of proteins, and hydrolysis of ATP) causes a detectable change in some electrical property of the cell that is characteristic of said event. The person of ordinary skill in the art would require extensive experimentation to determine the conditions under which, for example, mRNA transcription (certainly a cellular event) could be detected using the instant method. No criteria are suggested by the applicants for detecting this event, and no guidance is set forth for identifying acceptable criteria. The clear focus of the instant disclosure is the detection of signaling events initiated by receptors' interactions with their ligands; applicants provide no clear guidance for detecting any other type of event, and the prior art does not teach such detection.

Applicants present a single working embodiment comprising transfecting cells with cDNAs encoding one of a few GPCRs or a few PTKRs (paragraphs 0032-0033),

measuring the impedance of said cells in some undisclosed media within culture wells using several different electrical currents with several different frequencies (paragraphs 0030-0031), adding the ligand for the receptor being expressed in the cell to the culture well, again measuring impedance using the same electrical currents, and parametrizing the data into Legendre polynomials (Figures 4-12). At no point, however, do applicants exemplify creating a database with the data in Figures 4-12, comparing data from a test cell expressing an unknown receptor or a test cell contacted with a ligand of unknown function to said database, and determining which, if any, of the pathways exemplified in Figures 4-12 are activated in said test cell.

Only a few receptors were tested in a few cell types (three Gs-type receptors and three Gq-type receptors in CHO cells; three Gq-type receptors, two Gi-type receptors, and three PTKR-type receptors in HeLa cells), and only a few comparisons within these control data sets are exemplified (for example, the endothelin-1 Gq-type receptor in HeLa cells was compared to the CXCR4 Gi-type receptor in HeLa cells; Figure 10). Applicant has not provided "parameter sets of known messenger pathways" as required in step (f) of claims 1 and 12, and more importantly, the disclosure provides insufficient guidance such that the person of ordinary skill in the art would have a reasonable expectation of performing the method on a test cell expressing an unknown receptor or contacted with a ligand of unknown effect and using the "parameter sets" to obtain a reliable determination of the active pathways within the test cell. At best, applicants have enabled a method of determining whether one of the exemplified pathways is

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active within a test cell cultured under conditions identical to those disclosed in the specification.

While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23, 36, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Overall, claim 1 is vague and fails to particularly describe the method steps encompassed by the instant invention.

In claim 1, step (a) requires "measuring a value of an electrical property for at least one frequency within a range of frequencies for each time point." First, the requirement that "a value" of an electrical property be measured is not specific; it is simply not clear what is to be measured, e.g. the conductivity of the cell culture medium; the resistance of the cells themselves; and so on. Furthermore, the relationship between the frequency, the electrical property, and the cell is never particularly defined; indeed, it is not clear to what entity "frequency" refers. In addition, the limitation "each time point" fails to find basis anywhere in the claim. Furthermore, it is not clear whether

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"for at least one frequency..." and "for a cell with a receptor..." relates to the electrical property, the value of an electrical property, each other, or some other value. Finally, the limitation "receptor having a known receptor type and a known messenger pathway" is not particularly defined, since the set of receptors included by the claim and the set excluded by the claim are not clearly pointed out. Clarification is required.

In claim 1, step (b) requires selecting a time point "corresponding to" a time period, but the manner of this correspondence is not particularly pointed out.

Furthermore, step (b) recites "a known stimulus" but does not point out what is being stimulated (*i.e.*, the cell, the receptor, the electrical property, *etc.*); therefore, the metes and bounds of the claim are not particularly pointed out. Clarification is required.

In claim 1, step (c) requires "adding a known stimulus," but it is not clear to what the stimulus is "added" and how, if at all, said stimulus physically, chemically, electrically, or otherwise interacts with the cell and/or the receptor. Clarification is required. The examiner suggests the claim be amended to recite some sort of culture vessel and that the "adding" step require contact between the cell and/or the receptor and the stimulus.

In claim 1, step (d) requires subtracting various values "for each subsequent time point," but only one time point is particularly recited within the earlier steps. Similarly, step (e) refers to "each" time point, "each" receptor, and "each" stimulus, but the prior steps recite only one time point, one receptor, and one stimulus. Clarification is required.

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In claim 1, step (f) requires a comparison step but does not point out the particular comparisons required to classify cellular events. Clarification is required.

Because claims 2-11 and 36 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Overall, claim 12 is vague and fails to particularly describe the method steps encompassed by the instant invention. Step (a) requires "measuring impedance for at least one frequency within a range of frequencies for each time point." First, the relationship between the frequency, the electrical property, and the cell is never particularly defined. In addition, the limitation "each time point" fails to find basis anywhere in the claim. Furthermore, it is not clear whether "for at least one frequency..." and "for a cell with a receptor..." relates to the electrical property, the value of an electrical property, each other, or some other value. Finally, the limitation "receptor having a known receptor type and a known messenger pathway" is not particularly defined, since the set of receptors included by the claim and the set excluded by the claim are not clearly pointed out. Clarification is required.

In claim 12, step (b) requires selecting a time point "corresponding to" a time period, but the manner of this correspondence is not particularly pointed out.

Furthermore, step (b) recites "a known stimulus" but does not point out what is being stimulated (*i.e.*, the cell, the receptor, the electrical property, *etc.*); therefore, the metes and bounds of the claim are not particularly pointed out. Clarification is required.

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In claim 12, step (c) requires "adding a known stimulus," but it is not clear to what the stimulus is "added" and how, if at all, said stimulus physically, chemically, electrically, or otherwise interacts with the cell and/or the receptor. Clarification is required. The examiner suggests the claim be amended to recite some sort of culture vessel and that the "adding" step require contact between the cell and/or the receptor and the stimulus.

In claim 12, step (d) requires subtracting various values "for each subsequent time point," but only one time point is particularly recited within the earlier steps.

Similarly, step (e) refers to "each" time point, "each" receptor, and "each" stimulus, but the prior steps recite only one time point, one receptor, and one stimulus. Clarification is required.

In claim 12, step (f) requires a comparison step but does not point out the particular comparisons required to classify cellular events. Clarification is required.

Because claims 13-23 and 37 depend from indefinite claim 12 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph. Numerous dependent claims are further indefinite for the following reasons.

Claims 2 and 15 are in improper Markush form; a Markush group should be in the form "an event selected from the group **consisting of** A, B, and C". Currently, it is not clear which species are included in the Markush group and which are not, since the event must be chosen from a group "comprising" various events. "Comprising" is openended and does not exclude additional, unrecited members of a list. See M.P.E.P. §

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2111.03. Therefore, these claims have been interpreted as requiring that the cellular events be any cellular events.

Similarly, claim 3 requires that the electrical property be chosen from a group "comprising" various properties. See M.P.E.P. § 2111.03. Therefore, these claims have been interpreted as requiring that the electrical properties be any electrical properties.

Claims 7 and 21 require that the substance of claim 6 be a "small molecule ligand," which is confusing since it is not clear whether this limitation requires that the substance be a small molecule that is a ligand for some other molecule or whether that it be a ligand for a particular small molecule. Clarification is required.

Claims 9 and 23 require that the classification of claims 1 and 12 "be achieved in real time," which is confusing. It is not clear how "real time" would be determined for the actual "classification," which has been interpreted by the examiner as referring to the "comparing" step (step f) of claims 1 and 12. Clarification is required.

Claims 10, 11, 13, and 14 are confusing because they depend from claims 1 and 12 and require "further" steps, but seem to repeat the steps of claims 1 and 12 with minor modifications (*i.e.*, "unknown stimulus" and "unknown receptor"). It is not clear whether claims 10, 11, 13, and 14 are actually drawn to methods comprising steps (a)-(f) in addition to steps (g)-(l) or whether they are merely modifications of the parent claims. If the former is the case, it is not clear how steps (a)-(f) are related to steps (g)-(l). Clarification is required.

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It is not clear whether the "complex impedance" of claim 3 is the same as the "impedance" of claims 12-23 and 37. Clarification is required. In the interest of compact prosecution, these terms have been taken to be equivalents.

Claims 36 and 37 require that cells be "incorporated into an electrical circuit." It is not clear whether this is an active method step or whether this limitation simply describes the relationship of the cells to some electrical circuit. Furthermore, it is not clear how the electrical circuit relates to the frequency and the stimulus of claims 1 and 12. Clarification is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9, 12, 15-23, 36, and 37 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The claims have been interpreted as being drawn to a method comprising measuring an electrical property (in some cases, impedance) of a cell expressing a known receptor, contacting said cell with a known stimulus (in some cases, a ligand to the receptor), observing changes in the electrical property, and comparing said changes to data sets from cells in which known messenger pathways are activated in order to determine which receptor is active in the cell. The claims, in short, appear to describe a method for determining the active receptor within a cell expressing a known receptor; such a method is not useful, since the claims require that the cells express a known receptor (claim 1, step a), so a person

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practicing said method would know before carrying out the steps which receptor is activated.

Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Situations that require carrying out further research to identify or reasonably confirm a "real world" context of use do not define a substantial utility. See M.P.E.P. §2107.01 (I) (B). In this case, the cited claims appear to be drawn to a method of establishing a database that could at some point be used to determine what receptor is active in a cell with unknown receptors or in a cell contacted with a ligand whose effect is unknown, as described in claims 10, 11, 13, and 14, which are not included in this rejection, since they are drawn to identifying some unknown property of a cell, receptor, or ligand. Without these limitations, however, the cited claims cannot be considered to have substantial patentable utility.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-23, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wegener et al. (1999, European Journal of Physiology 437: 925-934; reference 7 on 3/1/04 IDS) taken in view of Rigaud et al. (1995, Physiological Measurement 16: A15-A28; reference U). The claims have been interpreted as being drawn to a method comprising measuring an electrical property (in some cases, impedance) of a cell expressing a known receptor in response to energy of various frequencies, contacting said cell with a known stimulus (in some cases, a ligand to the receptor), observing changes in the electrical property, and comparing said changes to data sets from cells in which known messenger pathways are activated in order to determine which receptor is active in the cell. In some dependent claims, the stimulus is a substance, in particular a small molecule, in particular a ligand. In some dependent claims, the cell expresses an unknown receptor or the stimulus is of unknown effect. In some dependent claims, the complex impedance, resistance, or admittance is measured. In some dependent claims, data is collected in real time. In some dependent claims, the cell is part of an electrical circuit. This rejection pertains to the embodiment in which the cellular event is signal transduction from ligand/receptor interactions and in which a characteristic result can be obtained from impedance measurements of cells.

Wegener et al. teach culturing bovine aorta endothelial cells (BAEC) in a monolayer, analyzing said cells with electric cell-substrate impedance sensing (ECIS), adding isoprotenerol or alprenolol to the culture medium (ligands for b-adrenoreceptor,

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which is expressed by BAEC), and conducting ECIS on the treated cells (page 927, column 1, paragraph 3, through column 2, paragraph 6; Figures 3-5).

Wegener et al. do not teach the range of frequencies recited in claims 5 and 19. Wegener et al. do not teach comparing the test cell to any standard.

Rigaud et al. teach analyzing numerous types of cells with ECIS with numerous frequencies (between 0.2kHz and 1MHz) applied thereto (Figure 1). Rigaud et al. further teach parametrizing the data from the ECIS experiments (Tables 1 and 2) and comparing the data from the various cell types to each other (Figure 3).

A person of ordinary skill in the art would have had a reasonable expectation of success in conducting the method of Wegener et al. using the range of frequencies of Rigaud et al. because Rigaud et al. teaches that ECIS may be carried out across a range of frequencies to produce a data set (Figure 1). The skilled artisan would have been motivated to conduct the method of Wegener et al. using numerous frequencies so as to obtain additional characterizing data for a particular cell.

The skilled artisan would have had a further reasonable expectation of success in conducting the method of Wegener et al. on numerous cell types or cells contacted with numerous ligands and comparing the results of these experiments because Rigaud et al. teach that such data sets are classifiable and comparable (Tables 1 and 2; Figure 3).

The selection of cell type, ligand, frequency, and/or electrical property in the method of Wegener et al. taken in view of Rigaud et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing

that Rigaud et al. teach that various types of cells can be investigated using ECIS, and various frequencies may be employed to conduct ECIS, and that Wegener et al. teach that ECIS may be used to study various ligands of diverse structure. Furthermore, since all electrical properties are related to each other by art-recognized equations, measurement of one variable is functionally and practically equivalent to measurement of any other variable. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the method of Wegener et al., which requires conducting ECIS on ligand-treated cells, with the method of Rigaud et al., which requires conducting ECIS on various cells at various frequencies and comparing the resulting data, because Wegener et al. and Rigaud et al. teach permutations of the same process, *i.e.* ECIS.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant should specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

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Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SANDRALE SALKDER

Lora E Barnhart

(Ob)